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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/664,127	09/18/2000	Wolfgang H. Dillmann	220002057202	9042

7590 01/31/2002

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1633	5

DATE MAILED: 01/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/664,127	DILLMANN ET AL.	
	Examin r	Art Unit	
	Shin-Lin Chen	1633	

-- The MAILING DATE of this communication appears on the c ver sheet with the c rrespondence address --

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *10-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-9* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of group I, claims 1-9, in Paper No. 3 is acknowledged. The traversal is on the ground(s) that no search burden is placed on examiner in searching all claims together because they fall with same class, 435. This is not found persuasive because a method of making an recombinant adenoviral vector comprising an adenoviral genome lacking E1A/E1B genes, a transgene coding a heat shock protein, and a promoter, and a method of elevating the level of stress related factor in the myocardium of a patient by delivering a replication-deficient viral vector expressing a stress related factor to said myocardium are different methods with different objectives, different starting materials and reagents, different method steps and response variables. Further, a stress related factor is not limited to heat shock protein and a viral vector is not limited to an adenoviral vector, and the method of elevating the level of stress related factor by using a viral vector expressing a gene product is classified in class 514, which is different from class 435.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 10-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 3.

Applicants' preliminary amendments filed 12-17-01 has been entered. Claims 1 and 9 have been amended. Claims 1-20 are pending and claims 1-9 are under consideration.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 2 recites the limitation "the adenosine A3 receptor" in line 2. There is insufficient antecedent basis for this limitation in the claim. An adenosine A3 receptor is not a heat shock protein, therefore, there is no antecedent basis in the claim for the phrase "the adenosine A3 receptor".

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for providing protection against simulated ischemia via adenovirus mediated gene transfer of a heat shock protein 70 (HSP 70) *in vitro*, wherein said adenovirus is an replication deficient adenovirus lacking E1A and E1B genes, does not reasonably provide

enablement for providing protection against myocardial ischemia by using adenovirus mediated gene transfer of a heat shock protein via any administration route *in vivo*, wherein said adenovirus is an replication deficient adenovirus lacking E1A and E1B genes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-4 are directed to an isolated recombinant adenoviral vector comprising an adenoviral genome lacking E1A/E1B genes, a transgene coding for a heat shock protein, and a promoter operably linked to said transgene. Claim 2 specifies the heat shock protein is HSP70i, HSP27, HSP40, or HSP60. Claims 3 and 4 specify the promoter is a CMV promoter or a ventricular myocyte-specific promoter.

The specification discloses preparation of a replication-deficient recombinant adenoviral vector lacking E1A and E1B genes and protection against simulated ischemia *in vitro* via said adenoviral vector mediated gene transfer of a heat shock protein 70 (HSP 70) by measuring the decrease of creatine kinase (CK) or lactate dehydrogenase (LDH) as compared to control (specification, page 20-26). The specification states "The present invention relates to a recombinant viral vector which is used in gene therapy for myocardial ischemia... and a method of producing myocardial protection during revascularization or non-revascularization procedures with the use of the vector" (specification, page 1). The claimed adenoviral vector must have a use for the present application. Therefore, the claims read on gene therapy *in vivo* by using the claimed recombinant adenoviral vector in light of the specification.

The specification fails to provide adequate guidance and evidence for delivering a recombinant adenoviral vector expressing a heat shock protein via different administration routes, such as oral administration, intravenous injection, intramuscular injection etc., to a particular myocardial site in a subject so as to provide protection against myocardial ischemia in a subject *in vivo*. The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101, 1996) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the

amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). The instant specification does not provide any *in vivo* working examples. The specification fails to teach how to deliver the recombinant adenoviral vector expressing a heat shock protein to a subject and sufficient amount of said protein is expressed in the targeted site so as to provide protection against myocardial ischemia in a subject *in vivo*.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden et al., 1997 (US Patent No. 5,658,729) in view of Hutter et al., 1994 (Circulation, Vol. 89, No. 1, p. 355-360) and Stege et al., 1994 (Experimental Cell Research, Vol. 214, No. 1, p. 279-284).

Claims 1-4 are directed to an isolated recombinant adenoviral vector comprising an adenoviral genome lacking E1A/E1B genes, a transgene coding for a heat shock protein, and a promoter operably linked to said transgene. Claim 2 specifies the heat shock protein is HSP70i, HSP27, HSP40, or HSP60. Claims 3 and 4 specify the promoter is a CMV promoter or a ventricular myocyte-specific promoter.

Hayden teaches preparation of a replication-deficient recombinant adenoviral vector lacking E1A or E1B genes and expressing lipoprotein lipase (LPL), and use of said adenoviral vector in gene therapy for treating LPL deficiencies. Hayden also teaches using RSV promoter or CMV promoter for the expression LPL gene product and suggest using a muscle-specific promoter in place of CMV promoter for the purpose of tissue-specific expression of gene of interest (e.g. column 1, 8).

Hayden does not teach using a recombinant adenoviral vector expressing a heat shock protein.

Hutter teaches heat shock treatment of rats results in the induction of HSP72 and a reduction of infarct size after subsequent ischemia and reperfusion and there is a direct correlation between the amount of HSP72 induced and the reduction in infarct size in rat, i.e. the degree of myocardial protection from ischemic injury (e.g. title, abstract).

Stege teaches the presence of the human HSP72 gene and the use of said HSP72 gene in transfecting Rat-1 fibroblast cells (e.g. abstract).

It would have been obvious for one of ordinary skill at the time of the invention to substitute the LPL gene with HSP72 gene as disclosed by Stege because it was well known in the art to replace a gene in a vector with another gene and Hutter teaches that HSP72 has positive effect in protecting myocardium from ischemic injury.

One ordinary skill at the time the invention was made would have been motivated to use a replication-deficient adenoviral vector expressing HSP72 for gene therapy to reduce infarct size and provide myocardial protection against ischemic injury as taught by Hutter and Hayden with reasonable expectation of success.

It should be noted that the full-length reference of Stege will be provided following this Official action.

10. Claims 5 and 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden et al., 1997, Hutter et al., 1994, and Stege et al., 1994 as applied to claims 1-4 above, and further in view of McGrory et al., 1988 (Virology, Vol. 163, p. 614-617).

Claims 5 and 7-9 are directed to a method of producing an isolated and purified recombinant vector of claim 1 by cloning a transgene coding for a stress related factor, such as HSP70i, HSP27, HSP40, or HSP60, into a plasmid containing a promoter, a polylinker flanked by left end of adenoviral 5 genome lacking E1A/E1B genes, co-transfecting said plasmid into mammalian cells transformed with the E1A/E1B genes with a plasmid containing the entire human adenoviral 5 genome with an insert making the plasmid too large to be encapsulated, and creating a recombinant genome containing the transgene without the E1A and E1B genes. Claim 7 specifies treating cell supernatant with proteinase K, followed by pheno/chloroform extraction and ethanol precipitation and identification via PCR amplification. Claim 8 specifies purifying the recombinant vectors by double CsCL gradient ultracentrifugation.

The collective teachings of Hayden et al., Hutter et al., and Stege et al. are as discussed in the previous section.

McGrory teaches construction of a plasmid, PJM17, containing the entire Ad5 DNA molecule, with an insert in the E1 region that exceeds the packaging constraints of the adenoviral capsid, and co-transfecting 293 cells, which expresses E1A and E1B, with said PJM17 plasmid and an E1-containing plasmid carrying mutated sequences to produce recombinant adenovirus virions at high efficiencies. Both E1A and E1B mutants as well as foreign gene inserts in the E1 region can be rescued into virus (e.g. abstract).

It would have been obvious for one of ordinary skill at the time of the invention to use the method taught by McGrory to prepare the recombinant adenoviral vector of claim 1 because of

the reasons discussed in previous section in preparing the adenoviral vector of claim 1 and McGrory teaches a method for preparing an adenoviral vector. It would have been obvious for one of ordinary skill because it was sell known in the art to treat cell supernatant with proteinase K, followed by pheno/chloroform extraction and ethanol precipitation to prepare viral vector and identify viral DNA via PCR amplification. It also was well known in the art to purify DNA or recombinant vectors by double CsCL gradient ultracentrifugation.

One ordinary skill at the time the invention was made would have been motivated to do so in order to prepare a replication-deficient adenoviral vector expressing HSP72 for gene therapy to reduce infarct size and provide myocardial protection against ischemic injury as taught by Hutter and Hayden with reasonable expectation of success.

Conclusion

11. Claims 1-5 and 7-9 are rejected. Claim 6 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

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